REMARKS

Applicant has carefully considered the matters raised by the Examiner in the outstanding Office Action but remains of the position that patentable subject matter is present. Applicant respectfully requests reconsideration of the Examiner's position based on the following remarks.

The present invention discloses a process for making cyclodextrin complexes using a precipitation method. In one of the novel aspects of the invention, a cyclodextrin-guest solution is formed where the cyclodextrin is present at a concentration of greater than about 15% by weight. Applicant has discovered that the process of the present invention controls yield, production efficiency and particle size better than conventional precipitation methods that employ cyclodextrin at a concentration of less than a 10% by weight.

Furthermore, it has surprisingly been found that the process of the present invention produces a desirable complex. One of skill in the art would expect that increasing the cyclodextrin concentration while employing a precipitation method would result in a large complex,

having a low yield and decreased efficiency. One of skill would expect such results because as a cyclodextrin-guest precipitate forms, the additionally added uncomplexed cyclodextrin would be presumed to cling to the formed cyclodextrin-guest precipitate thus increasing the overall size of the precipitate (page 5, lines 7-17). As a result of this presumption, conventional precipitation techniques limit the cyclodextrin concentration to less than 10% by weight (page 3, lines 6-8). Applicant has surprisingly discovered that such expected phenomenon do not occur according to the method of the present invention.

This Application discloses two methods for increasing the concentration of cyclodextrin in solution. First, heating the solution during its formation to 60 to 100°C (page 6, line 2), maintaining the temperature during the mixing step (page 8, line 11) and cooling the solution to atmospheric temperature to promote precipitation (page 9, line 4). The second method for increasing the concentration of cyclodextrin is to adjust the pH to 11 to 13 during formation and adjusting the pH back to neutral after adding the guest (page 6, lines 5-11).

In order to highlight these aspects of the present invention, claim 1 has been amended to recite the temperature changes while claim 5 has been amended to recite the pH changes.

Claims 1-8 are pending in this Application. Claims 1-8 had been rejected as being unpatentable over Hedges. Claims 3 and 7 had been rejected under 35 USC 112, second paragraph, as being indefinite for using the term "modified" cyclodextrin without reference to the specific modifications.

Hedges teaches the production of cyclodextrin complexes using the coprecipitation, slurry, paste and dry mixing methods. The Examiner had appeared recognize that Hedges does not teach the claimed cyclodextrin concentration with respect to the coprecipitation method. Instead, the Examiner had referred to Hedges' description of the slurry method for teaching a cyclodextrin concentration of 40-45% (page 2035, col. 2, paragraph 2). In addition, the Examiner had referred to a later section

of Hedges where the prodrug Pilocarpine is complexed[1] with cyclodextrin at a concentration of 15% (page 2041, col. 1, paragraph 6).

The Examiner had made the ultimate conclusion that it would be obvious to "modify" or "scale-up" the coprecipitation process of Hedges to increase the yield of the complex (page 4, lines 8-18 of Office Action). The Examiner had also stated that one skilled in the art "would assume" that the 15% cyclodextrin-Pilocarpine complex is useful when formed by a precipitation method (page 6, lines 5-12 of Office Action). Applicant respectfully disagrees with the Examiner's reasoning.

One of skill in the art would not be motivated to modify the coprecipitation technique of page 2035 of Hedges based on the teachings of Hedges. As mentioned above, page 5, lines 7-17 of the Application specifically explain that one of skill would expect that increasing the cyclodextrin concentration while employing a precipitation method would result in an unacceptably large complex, having a low yield

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[1] This section of Hedges does not explain which complexation technique was employed.

and decreased efficiency. The Examiner's reasoning, however, directly contradicts this statement. The Examiner had stated that one of skill "would assume" that the coprecipitation method of Hedges can be "scaled-up" in order to arrive at the present invention. This simply is not true. On the contrary, one of skill in the art would in fact assume that a scale-up of the coprecipitation method of Hedges would produce an unacceptable complex. This is precisely the reason why Hedges discloses alternative complexation methods, such as the cited slurry method, where higher concentrations of cyclodextrin are known to be successful. In contrast to the teachings of Hedges and the conventional knowledge in the art, Applicant has surprisingly discovered that a desirable complex can be formed by the precipitation method of the present invention. Such a finding is in contradiction to what one of skill in the art would "assume".

Furthermore, there is no indication that the cited cyclodextrin-Pilocarpine complex of Hedges was formed by the precipitation method of the present invention. In fact, absent a specific teaching to the contrary, one of skill would assume that the cyclodextrin-Pilocarpine complex was produced by a method other than the

precipitation method, since one of skill would assume that the precipitation method is not feasible at cyclodextrin concentrations above 10% by weight (page 3, lines 6-8 of Application).

Applicant therefore respectfully submits that one of skill in the art would not be motivated to modify the coprecipitation method of Hedges to arrive at the present invention. Applicant submits that one of skill in the art would in fact be motivated to look to other complexation methods, such as the slurry method disclosed in Hedges, if it were desired to increase the cyclodextrin concentration.

Furthermore, in order to distinguish the present invention, the claims have been amended to recite how the concentration is increased. Hedges does not teach the specific heating cycle of pH cycle of the amended claims.

Turning now to the remaining rejection, the Examiner had stated that the term "modified" cyclodextrin as used in claims 3 and 7 is a relative term that renders the claim indefinite. The Examiner had required that Applicant identify the specific structural modifications in order to determine the scope of the modified cyclodextrin.

Applicant respectfully submits that a detailed recitation of the specific structural modifications of cyclodextrin is not necessary under the circumstances. As explained on page 2, lines 16-21 of the Application, a modified cyclodextrin is a cyclodextrin that has been altered to increase it's hydrophilic nature. One of skill in the art is fully aware that a modified cyclodextrin is a cyclodextrin that has been modified at the 2-, 3-, or 6-position to increase solubility. For example, Hedges contains such an explanation of modification (page 2037, col. 2, paragraph 2), as does the enclosed website printout. Thus, the scope of the modified cyclodextrin as used in the present invention is indeed readily understandable by one of skill in the art. Applicant respectfully requests that this ground of rejection be removed.

In view of the foregoing and the enclosed, it is respectfully submitted that the application is in condition for allowance and such action is respectfully requested. Should any extensions of time or fees be necessary in order to maintain this Application in pending condition,

appropriate requests are hereby made and authorization is given to debit Account # 02-2275.

Respectfully submitted,

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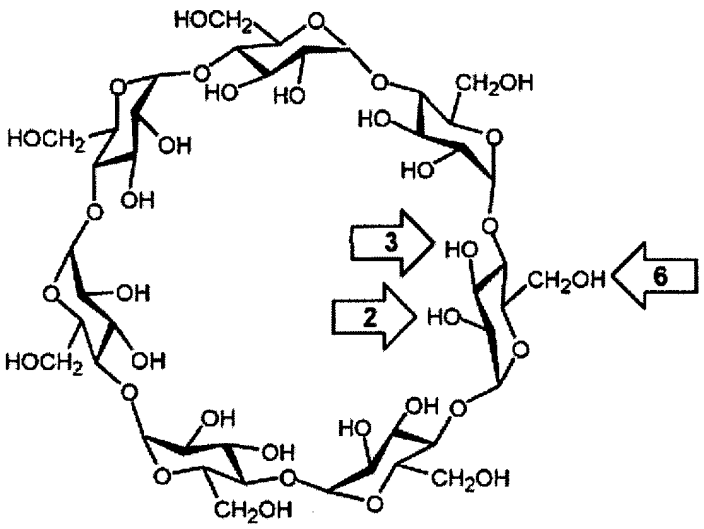
CYCLODEXTRINS GENERAL

What are cyclodextrins?

Cyclodextrins are cyclic oligosaccharides typically containing 6(α-CD), 7(β-CD), or 8(γ-CD) glucopyranose units. This cyclic orientation provides a truncated cone structure that is hydrophilic on the exterior and lipophilic on the interior. Cyclodextrin complexes are formed when a guest molecule is partially or fully contained in the interior of the cavity. The parent α-, β-, and γ-cyclodextrins (particularly β) have limited aqueous solubility and show toxicity when given by injection. Therefore, the parent cyclodextrin structure has been chemically modified to generate a parenterally safe CD-derivative. The modifications are typically made at one or more of the 2, 3, or 6 position hydroxyls.



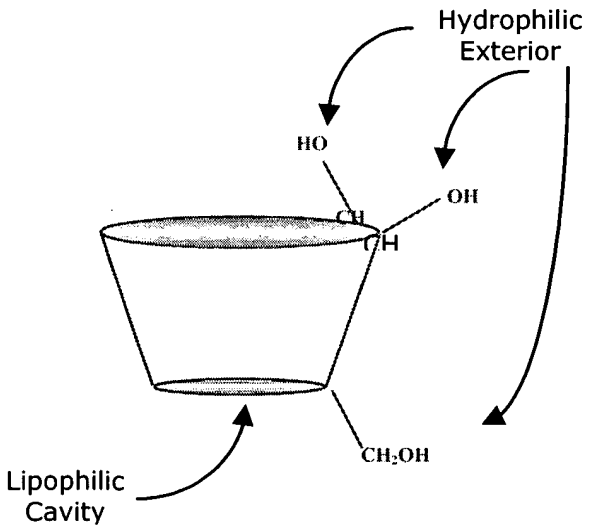
What is the difference between dextrins and dextrans?

Dextrans are soluble polysaccharides produced by bacteria and yeasts. They are characterized by a predominance (>95%) of α (1-6) backbone linkages and varying proportions of α(1-2), α(1-3) and α(1-4) linkages typically at branch points[1,2].

Dextrins are partially hydrolyzed glucose homopolymers composed exclusively of α(1-4) backbone linkages.

β-cyclodextrin is a cyclic structure composed of seven glucose units linked by α(1-4) linkages. Therefore it is a dextrin.

[1]Lehninger, A.L., (1975) Biochemistry, 2nd edition, pp. 264-266, Worth, New York.
[2]Janson, J., (1972) Studies on dextran degrading enzymes from bacterial and molds, PhD dissertation, Uppsala University, Sweden



What are modified cyclodextrins and why were they developed?

Chemical modifications have been made by numerous researchers to alter the undesirable solubility and parenteral safety properties of the parent cyclodextrins. The modifications are mostly derivatives attached through the three available hydroxyl groups on each glucopyranose unit. Thus up to 18(α-CD), 21(β-CD), or 24(γ-CD) degrees of substitution may be realized, with numerous positional and regioisomers possible.